Int. J. Cancer: **117,** 281–288 (2005)

Thyroid cancer and multiple primary tumors in the SEER cancer registries[1]

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Thyroid cancer incidence rates have increased steadily in the United States and elsewhere. Radiation exposure at a young age is a strong risk factor, but otherwise the etiology is unclear. To explore etiologic clues, we studied the risk of thyroid cancer after an earlier primary cancer, as well as the risk of developing multiple primaries after an earlier thyroid cancer in the U.S. Surveillance, Epidemiology and End-Results (SEER) cancer registries program (1973–2000). In 2,036,597 patients diagnosed with any invasive cancer who survived for a minimum of 2 months, we observed a 42% increased risk compared to the general population for second thyroid cancer based on 1,366 cases (95% confidence interval (CI) = 35–50%; excess absolute risk (EAR) = 0.38/10,000 person-years (PY)). Elevated risks were observed after most cancer sites studied. The most pronounced excess (observed/expected (O/E) = 2.86) was seen for second thyroid cancers detected in the year after diagnosis of the first cancer. Among 29,456 2-month thyroid cancer survivors, 2,214 second cancers occurred (O/E = 1.11, 95% CI = 1.06–1.15; EAR = 7.64/10,000 PY). Again, the highest risk was seen in the first year (O/E = 1.26). Patients <40 years of age at diagnosis of thyroid cancer had a 39% increased risk of a second cancer, whereas for older patients the risk was elevated 6%. We observed consistently increased risks for cancers of the breast, prostate, and kidney, and a likely radiation treatment-related excess of leukemia. Based on small numbers of cases, cancers of the salivary glands, trachea, scrotum, adrenal glands, and brain and central nervous system (CNS) also occurred in excess. A decreased risk was observed for smoking-related malignancies. Thyroid cancer is associated with primary cancers of many different organs. Although enhanced medical surveillance likely plays a role, 2-way, positive associations between thyroid cancer and cancers of the breast, prostate, kidney, salivary glands, brain and CNS, scrotum, and leukemia suggest etiologic similarities and possible treatment effects.

Key words: multiple primary cancers; thyroid cancer; epidemiology; radiotherapy

Approximately 1.5% of new cancers diagnosed in the United States in 2001 were malignancies of the thyroid gland. While the incidence rates are low, they have been increasing over recent decades in many areas of the world.[1] In the United States, about 90% of thyroid cancers are papillary or follicular adenocarcinoma, while anaplastic and medullary cancers account for less than 5% each.[2] The 10-year relative survival rate for thyroid cancer is close to 95%,[3] although the prognosis for anaplastic thyroid cancer is dismal, with few patients surviving beyond 1 year.[4] The demographic characteristics of thyroid malignancies are different from most other cancers. There is a 1:3 male-female ratio and an unusual age distribution.[1] Unlike other malignancies, female thyroid cancer rates increase steeply from the mid-teens until age 50, i.e., around menopause, and steadily decrease thereafter. In males, the early increase is less steep and continues through age 70.[1] As a result, the male-female ratio is most pronounced during the female reproductive period. These observations coupled with other epidemiologic findings[5] suggest that sex hormones play a role in female thyroid carcinogenesis, but so far a unifying mechanism has not been defined.[6]

Exposure to ionizing radiation at a young age is a strong and established risk factor for papillary thyroid cancer and, to a lesser extent, follicular thyroid cancer.[7] A history of thyroid disease, notably benign nodules, is also associated with increased thyroid cancer risk.[8] A very small proportion of nonmedullary thyroid cancers have been associated with family cancer syndromes such as Cowden's syndrome[9] and familial adenomatous polyposis (FAP),[10] but familial clustering unrelated to known cancer syndromes has also been described.[10–12] The current study aims to describe and quantify the occurrence of thyroid cancer in conjunction with other malignancies.

Material and methods

We evaluated the risk for subsequent cancers among survivors of thyroid cancer, as well as the patterns of risk for thyroid cancer as a second primary after any other cancer in the population-based cohort of cancer survivors from the U.S. Surveillance, Epidemiology and End-Results (SEER) program.[13] The SEER program collects data on all persons diagnosed with cancer residing in several geographically defined regions where reporting to cancer registries is mandated by law. Quality control, with a required 98% case ascertainment, is conducted annually in all SEER registries. The SEER database includes information on patient demographics, as well as tumor site, histology, date of diagnosis, source of diagnosis, date of death, and first course of treatment for each recorded malignancy. Our study uses data from the original 9 SEER registries[1] that collectively cover 9% of the U.S. population and have sufficient follow-up time for evaluating second primaries.[3]

Cancer patients who were diagnosed with an invasive tumor between 1973 and 2000 and who survived at least 2 months after initial diagnosis are included in the present analyses. Nonmelanoma skin cancers and secondary cancers developing within the first 2 months after diagnosis were excluded from our analyses. All other secondary invasive malignant neoplasms (second, third, fourth, etc., cancers) were ascertained through linkage with cancer registry incidence files.

[1]SEER-9 includes the following regions: Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Utah, Seattle-Puget Sound, Atlanta.

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; CNS, central nervous system; E, expected number of cancer cases; EAR, excess absolute risk; FAP, familial adenomatous polyposis; ICD-O, International Classification of Diseases in Oncology; O, observed number of cancer cases; O/E, observed/expected ratio; PY, person-years; SEER, Surveillance, Epidemiology and End-Results. TSH, thyroid stimulating hormone.

Grant sponsor: Research & Development Office for Health and Personal Social Services in Northern Ireland (to PM).

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Received 17 September 2004; Accepted after revision 26 January 2005
DOI 10.1002/ijc.21064
Published online 4 May 2005 in Wiley InterScience (www.interscience.wiley.com).

Person-years (PY) at risk in the study cohort were accumulated by age, ethnic group (whites/unknown, blacks, other), sex, and calendar year periods from 2 months after the date of diagnosis of the first cancer to the date of either last follow-up, death, or December 31, 2000, whichever occurred first. Site-specific cancer incidence rates from the U.S. population were obtained from SEER by ethnic group, sex, 5-year age groups, and 5-year calendar periods, and were multiplied by the accumulated PY in the study cohort to estimate the expected number of cancer cases. The total number of observed (O) and expected (E) multiple cancers were then summed, with the relative risk defined as the ratio of observed and expected cases (O/E). Statistical tests and 2-sided 95% confidence intervals (CIs) were based on the assumption that the observed numbers of multiple tumors follow a Poisson distribution. To compute the excess absolute risk (EAR) of secondary cancers, that is, the average additional number of cancer patients per 10,000 cancer survivors per year, the expected number was subtracted from the number of observed cases, and the difference divided by the PY at risk. The number of excess cases was then expressed per 10,000 PY. For sex-specific cancers, PY for the respective sex were used. We repeated all analyses, excluding secondary cancers identified through autopsy or death certificate only. Histologic subtypes of differentiated thyroid cancer were defined based on the International Classification of Diseases in Oncology, second revision (ICD-O-2)[14] as follows: papillary (8050, 8260, 8340, 8350, 8450), follicular (8290, 8330–8332), and medullary (8510, 8511).

Results

Secondary thyroid cancer after any first cancer

The analyses of second primary thyroid cancer risk were based on a cohort of 2,036,597 eligible 2-month cancer survivors registered in SEER. The cohort was 51% male and 86% white (Table I). The median follow-up was 3 years, 19% of the cohort having more than 10 years follow-up after initial cancer diagnosis, and only 4% more than 20 years. Male cancer survivors were, on average, older at first cancer diagnosis than females (median = 67.0 *vs.* 64.3 years, respectively) and were followed for a shorter period (median = 2.6 *vs.* 3.6 years, respectively). Among the 1,366 patients with secondary thyroid cancer, the 5 most common first cancer sites included female breast (n = 345), prostate (n = 133), colon (n = 97), melanoma (n = 93), and lung (n = 84). The overall risk of thyroid cancer after any malignancy was 42% higher than expected (Table II), with significant excesses observed for both males and females (data not shown). The EAR was 0.38/10,000 PY. White (O = 1,144, O/E = 1.38, 95% CI = 1.30–1.46) and black (O = 66, O/E = 1.46, 95% CI = 1.13–1.85) cancer survivors were at equal risk of thyroid cancer, although patients of other ethnic groups (O = 156, O/E = 2.12, 95% CI = 1.80–2.47) seemed to be at slightly higher risk. The most pronounced excess (O = 342, O/E = 2.86, 95% CI = 2.56–3.18) was for thyroid cancers detected in the year after the initial cancer diagnosis, although long-term (≥10 years) cancer survivors also remained at greater risk than the general population (O = 260, O/E = 1.21, 95% CI = 1.07–1.37). Elevated secondary thyroid cancer risks were seen for most cancer sites listed in Table II, including the upper aerodigestive tract, liver, pancreas, female breast, male genital organs, kidney, melanoma, brain and central nervous system (CNS), thyroid, bone and soft tissue, and Hodgkin lymphoma and leukemia. The diagnosis of 180 (13.2%) secondary thyroid cancers was based solely on autopsy findings or death certificate, compared to 2.6% of all thyroid cancers registered in SEER. When excluded, the risk of secondary thyroid cancer after any cancer decreased slightly (O/E = 1.29, 95% CI = 1.22–1.37), but remained statistically significant, a pattern also seen after cancers of the buccal cavity, salivary glands, kidney, and leukemia. Previously high thyroid cancer risks after cancers of the esophagus (O/E=1.13), stomach (O/E = 1.20), liver (O/E = 2.51), pancreas (O/E = 0.79), lung (O/E = 1.32), scrotum (O/E = 8.42), and brain and CNS (O/E = 1.75) decreased substantially and were no longer statistically significant.

Patients with 2 thyroid cancers (O = 50) might have had recurrent disease instead of new primary tumors. In all, 30 patients had 2 papillary tumors, 1 patient had 2 follicular tumors, and another 14 patients had combinations of papillary and either follicular or unspecified carcinoma. In clinical practice, the second thyroid cancers diagnosed in these 45 patients would usually be classified as recurrences rather than new primary tumors. The remaining 5 patients were diagnosed with thyroid tumors that would be defined as independent primary cancers, i.e., papillary/medullary (n = 3), follicular/medullary (n = 1), and papillary/mucinous adenocarcinoma (n = 1). When we repeated the analyses of secondary thyroid cancer among 2-month cancer survivors excluding all individuals with a first thyroid cancer, the results were similar (O/E = 1.41).

Secondary cancers after a first thyroid cancer

Second cancers occurring among 29,456 2-month survivors of thyroid cancer were analyzed in a subgroup of the cohort described above (Table I). In contrast to the entire SEER cohort, only 25% of the thyroid cancer patients were male, the median age at first cancer diagnosis was 43 years, and the median follow-up was approximately 8 years. A considerable proportion of thy-

TABLE I – SELECTED CHARACTERISTICS OF 2-MONTH CANCER SURVIVORS BY TYPE OF FIRST CANCER[1]

Characteristic	First cancer survivor cohort			
	Any cancer (n = 2,036,597)		Thyroid cancer (n = 29,456)	
	n	(%)	n	(%)
Sex				
Male	1,038,089	(51)	7,406	(25)
Female	998,508	(49)	22,050	(75)
Race				
White	1,750,525	(86)	24,578	(83)
Black	171,501	(8)	1,536	(5)
Other	105,076	(5)	3,116	(11)
Unknown	9,495	(<1)	226	(<1)
Multiple cancers				
1	152,616		1,817	
2	14,078		158	
3 or more	1,481		27	
Any radiation treatment[2]	630,680	(31)	11,218	(38)
Median age at first cancer diagnosis (yrs)	65.9		43.2	
Median follow-up time (yrs)	3.0		7.9	

[1]U.S. SEER cancer registries, 1973–2000.–[2]Refers to radiation as first course of treatment only.

TABLE II – OCCURRENCE OF SECOND CANCERS FOLLOWING A FIRST PRIMARY THYROID CANCER, AND OCCURRENCE OF SECOND PRIMARY THYROID CANCER[1]

Other primary tumor	Risk of second primary thyroid cancer following any other cancer				Risk of a second primary cancer following thyroid cancer			
	O	O/E	95% CI	EAR[2]	O	O/E	95% CI	EAR[2]
All Sites[3]	1366	1.42[4]	1.35 – 1.50	0.38	2214	1.11[4]	1.06 – 1.15	7.64
Buccal cavity	42	1.70[4]	1.22 – 2.29	0.54	37	0.82	0.58 – 1.13	−0.29
Salivary gland	11	3.26[4]	1.63 – 5.84	1.94	13	2.78[4]	1.48 – 4.75	0.30
Pharynx	5	1.63	0.52 – 3.79	0.49	7	0.90	0.36 – 1.86	−0.03
Esophagus	6	3.17[4]	1.16 – 6.89	1.64	9	0.56	0.26 – 1.07	−0.25
Stomach	15	1.83[4]	1.02 – 3.01	0.71	43	1.21	0.88 – 1.63	0.27
Small intestine	3	1.47	0.29 – 4.29	0.40	9	1.42	0.65 – 2.70	0.09
Colon	97	1.16	0.94 – 1.42	0.14	182	1.06	0.92 – 1.23	0.39
Rectum	40	1.06	0.75 – 1.44	0.05	66	0.93	0.72 – 1.19	−0.17
Liver	6	7.07[4]	2.58 – 15.38	4.79	14	1.01	0.55 – 1.69	0.00
Gallbladder	0	—	0.00 – 4.23	−0.96	3	0.48	0.10 – 1.41	−0.12
Pancreas	12	4.48[4]	2.31 – 7.82	2.96	36	0.77	0.54 – 1.07	−0.38
Larynx	25	2.22[4]	1.44 – 3.27	0.88	10	0.61	0.29 – 1.13	−0.23
Lung and bronchus	84	2.10[4]	1.67 – 2.60	0.91	238	0.87[4]	0.76 – 0.99	−1.26
Trachea	1	10.32	0.13 – 57.43	7.84	5	14.47[4]	4.66 – 33.77	0.17
Female breast[5]	345	1.31[4]	1.18 – 1.46	0.35	530	1.21[4]	1.11 – 1.32	4.36
Cervix[5]	26	0.92	0.60 – 1.34	−0.10	21	0.68	0.42 – 1.04	−0.47
Uterine corpus[5]	62	0.84	0.64 – 1.08	−0.17	73	0.84	0.66 – 1.06	−0.64
Ovary[5]	32	1.36	0.93 – 1.92	0.41	55	0.99	0.74 – 1.28	−0.04
Prostate[5]	133	1.21[4]	1.01 – 1.43	0.15	257	1.31[4]	1.16 – 1.48	9.00
Testis[5]	12	1.98[4]	1.02 – 3.46	0.41	7	1.88	0.75 – 3.87	0.48
Scrotum[5]	3	11.58[4]	2.33 – 33.83	6.51	3	8.13[4]	1.63 – 23.75	0.39
Bladder	45	0.96	0.70 – 1.28	−0.03	62	0.84	0.65 – 1.08	−0.41
Kidney	45	2.93[4]	2.14 – 3.92	1.50	84	2.26[4]	1.80 – 2.79	1.67
Renal pelvis	3	1.51	0.30 – 4.41	0.41	8	2.11	0.91 – 4.16	0.15
Melanoma	93	2.01[4]	1.62 – 2.47	0.91	78	1.24	0.98 – 1.55	0.54
Brain and CNS	14	2.19[4]	1.20 – 3.68	0.72	37	1.54[4]	1.09 – 2.12	0.46
Thyroid	50	1.68[4]	1.25 – 2.21	0.72	50	1.68[4]	1.25 – 2.21	0.72
Adrenal gland	0	—	0.00 – 12.49	−0.48	4	4.72[4]	1.27 – 12.09	0.11
Bones and joints	5	2.48	0.80 – 5.80	0.93	6	2.50	0.91 – 5.44	0.13
Soft tissue	14	2.39[4]	1.30 – 4.00	1.00	13	1.41	0.75 – 2.42	0.14
NHL	38	1.29	0.91 – 1.77	0.24	71	0.99	0.77 – 1.25	−0.03
Hodgkin lymphoma	32	3.03[4]	2.07 – 4.28	1.43	14	1.67	0.91 – 2.81	0.20
Multiple myeloma	9	1.55	0.71 – 2.94	0.45	32	1.44	0.99 – 2.03	0.35
Leukemia	39	2.52[4]	1.79 – 3.45	1.01	62	1.39[4]	1.07 – 1.79	0.63

[1]U.S. SEER cancer registries, 1973–2000.–[2]Absolute Excess Risk = (O-E)/10,000 PY.–[3]excluding non-melanoma skin cancer.–[4]95% confidence interval does not include 1.0.–[5]For sex-specific cancers based on respective PY only.–O, observed number of cases; O/E ratio, observed over expected number of cases; CI, confidence interval.

roid cancer survivors were followed for more than 20 years (13%), highlighting the good prognosis of thyroid cancer and the young age at diagnosis. Most thyroid tumors were papillary (78%) or follicular (15%) adenocarcinomas. The first course of treatment was surgery for 95% of patients, but 38% of patients had any form of radiation treatment, usually in conjunction with surgery. Male thyroid cancer patients were older at thyroid cancer diagnosis than their female counterparts (47.6 *vs.* 42.0 years) and had a slightly shorter follow-up period (7.4 *vs.* 8.0 years). Among thyroid cancer survivors, 2,214 secondary malignancies occurred (Table II), corresponding to an 11% elevated risk compared to the general population and an EAR of 7.64/10,000 PY. Of those, 1,468 occurred among women (O/E = 1.10, 95% CI = 1.04–1.16) and 746 among men (O/E = 1.13, 95% CI = 1.05–1.21). The overall finding was mirrored for whites (O = 1,902, O/E = 1.11, 95% CI = 1.06–1.16) and patients of other ethnic groups (O = 177, O/E = 1.11, 95% CI = 0.95–1.28), but blacks had a slightly higher risk (O = 134, O/E = 1.31, 95% CI = 1.10–1.55). Results were comparable for papillary (O = 1,617, O/E = 1.11, 95% CI = 1.06–1.16) and follicular (O = 434, O/E = 1.08, 95% CI = 0.98–1.19) thyroid cancers. No increased risk was seen among 884 survivors of medullary tumors (O = 61, O/E = 0.83, 95% CI = 0.63–1.06). The highest excess was observed for second cancers diagnosed in the same year as the initial thyroid malignancy (O = 160, O/E = 1.26, 95% CI = 1.07–1.47), compared to the periods 1–4 years (O = 619, O/E = 1.17), 5–9 years (O = 590, O/E = 1.11), and more than 10 years (O = 845, O/E = 1.04) after diagnosis. This effect faded, however, when we excluded 50 second cancers of the thyroid gland, with O/E ratios of 1.13, 1.18, 1.12, and 1.03 for the respective latency periods. Relative risks exceeding 2 were observed for kidney and salivary gland cancer, and for several rare tumors (<5 expected cases), i.e., renal pelvis, bones and joints, adrenal gland, trachea, and scrotum (Table II). Only 9 secondary cancer diagnoses were based on autopsy or death certificate information.

Cancer sites positively associated with thyroid cancer in both directions

We observed an association between thyroid cancer and cancers of the breast, prostate, kidney, salivary glands, scrotum, brain and CNS, and leukemia, irrespective of which cancer occurred first. Breast cancer contributed 36% of all second cancers after female thyroid cancer, accounting for a 1.2-fold elevated risk compared to the general U.S. population (O = 530). O/E ratios for breast after thyroid cancer were elevated throughout the follow-up period (not shown) and were 1.42 (95% CI = 1.19–1.68) and 1.15 (95% CI = 1.04–1.27), respectively, for young (<40 years, O = 135) and older (≥40 years, O = 395) women at thyroid cancer diagnosis (Table III). Among 503 women with breast cancer after thyroid cancer, 25 (5%) had 2 malignant breast tumors and 1 woman had 3 malignant breast tumors. Breast cancer risk was comparable for papillary and follicular thyroid cancer survivors (O/E = 1.25 and 1.13, respectively). Reciprocally, breast cancer survivors had 1.3-fold risk of developing a second primary thyroid cancer (O =

TABLE III – OCCURRENCE OF THYROID CANCER AS THE FIRST OR SUBSEQUENT PRIMARY CANCER BY AGE AT DIAGNOSIS OF THE FIRST CANCER FOR SELECTED TUMOR SITES[1]

Other primary tumor	Age at first cancer diagnosis (yrs)							
	Risk of second primary thyroid cancer following any other cancer[2]				Risk of a second primary cancer following thyroid cancer[3]			
	<40		≥40		<40		≥40	
	O	O/E	O	O/E	O	O/E	O	O/E
All Sites[4]	225	2.06[5]	1141	1.34[5]	397	1.39[5]	1817	1.06[5]
Salivary gland	6	7.42[5]	5	1.95	6	5.99[5]	7	1.90
Stomach	1	3.54	14	1.76	7	2.65[5]	36	1.09
Colon	4	1.90	93	1.14	19	1.75[5]	163	1.02
Lung and bronchus	3	3.02	81	2.08[5]	20	1.03	218	0.86[5]
Female breast[6]	30	1.28	315	1.32[5]	135	1.42[5]	395	1.15[5]
Uterine corpus[6]	5	1.55	57	0.81	10	0.81	63	0.85
Ovary[6]	10	1.87	22	1.21	11	0.89	44	1.01
Prostate[6]	0	—	133	1.21[5]	12	1.84	245	1.29[5]
Bladder	3	1.90	42	0.92	6	1.21	56	0.82
Kidney	6	5.49[5]	39	2.74[5]	12	2.47[5]	72	2.23[5]
Melanoma	26	1.81[5]	67	2.11[5]	27	1.26	51	1.23
Brain and CNS	6	1.81	8	2.61[5]	16	2.78[5]	21	1.15
Thyroid	28	1.98[5]	22	1.41	28	1.98[5]	22	1.41
Adrenal gland	0	—	0	—	2	10.20[5]	2	3.07
Hodgkin lymphoma	31	4.08[5]	1	0.34	9	2.08	5	1.24
Leukemia	14	6.67[5]	25	1.87[5]	10	1.74	52	1.34[5]

[1]U.S. SEER cancer registries (1973–2000).–[2]All cancer cohort excluding non-melanoma skin cancer, age diagnosis <40 yrs: 1,343,175 PY; ≥40 yrs: 9,464,871 PY.–[3]Thyroid cancer survivors cohort, age at diagnosis <40 yrs: 135,756 PY : ≥40 yrs: 144,824 PY.–[4]Excluding non-melanoma skin cancer.–[5]95% confidence interval does not include 1.0.–[6]For sex-specific cancers based on respective PY only.–O, observed number of cases; O/E ratio, observed over expected number of cases; CI, confidence interval.

345) (Table II), with no variation by age at breast cancer diagnosis (Table III).

Prostate cancer was the most common second cancer among male thyroid cancer survivors, with 257 observed cases for a 1.3-fold increased risk (Table II). Most cases (O = 164) occurred within 10 years of thyroid cancer diagnosis, yielding a 1.46-fold risk (95% CI = 1.24–1.70), whereas the relative risk was 1.12 (95% CI = 0.90–1.37) and no longer statistically significant among long-term survivors (O = 93). The excess was seen for both young (O = 12, O/E = 1.84, 95% CI = 0.95–3.21) and old (O = 245, O/E = 1.24, 95% CI = 1.14–1.47) men at thyroid cancer diagnosis (Table III). Reciprocally, prostate cancer patients were themselves at slightly increased risk of thyroid cancer (Table II). The excess was most pronounced in the first year after prostate cancer diagnosis (O = 27, O/E = 1.70, 95% CI = 1.12–2.47), although a nonsignificant 51% increase (95% CI = 0.86–2.45, O = 16) was also seen in the relatively small group of 10-year survivors, which included 14% of all prostate cancer patients (not shown).

After thyroid cancer, we observed an excess risk of kidney cancer (O = 84, O/E = 2.26) (Table II), which did not seem to vary appreciably by age (Table III), sex, time interval since diagnosis, or histologic subtype of thyroid cancer (not shown). Thyroid cancer patients also were at increased risk of renal pelvis (O = 8, O/E = 2.11), but not bladder cancer (O = 62, O/E = 0.84) (Table II). Reciprocally, among patients with urinary tract cancers, only kidney cancer conferred a markedly increased risk of a subsequent thyroid cancer (O = 45, O/E = 2.93) (Table II).There was, however, a sharp gradient in risk with time since kidney cancer diagnosis, with O/E ratios for thyroid cancer decreasing from 7.57 (95% CI = 4.23–12.48) in the first year (O = 15) to 1.57 (95% CI = 0.51–3.67) among 10-year survivors (O = 5). Several other noteworthy second cancer patterns emerged among thyroid cancer survivors, although based on much smaller numbers of observations (Table II). There was a large increased risk of salivary gland cancer (O = 13, O/E = 2.78) and also an elevated reciprocal risk of thyroid cancer among salivary gland cancer survivors (O = 11, O/E = 3.26) (Table II). Similarly, we observed an 8-fold increased risk for scrotal cancer (O = 3) and an 11-fold reciprocal risk (O = 3), including one autopsy-based diagnosis. Melanoma risk was elevated (O = 78, O/E = 1.24), but, as noted for several other cancers, the risk was strongest in the first year after thyroid cancer diagnosis (O/E = 1.91) and decreased steadily thereafter to 1.07 among 10-year survivors. Survivors of melanoma also had a significantly increased risk of thyroid cancer (O = 93, O/E = 2.01). Again, risk decreased with increasing follow-up, from 4.70 in the first year (O = 20) to 1.52 (O = 20) among 10-year survivors. In addition, a highly increased risk of tracheal cancer after thyroid cancer was observed (O = 5, O/E = 14), and adrenal cancers occurred in excess (O = 4, O/E = 4.72) (Table II), in particular after medullary thyroid cancer (O = 2, O/E = 70.42).

Treatment for first malignancy

Radiotherapy is known to contribute to second tumor risk mainly among long-term (>10-year) cancer survivors.[15,16] Unlike most other malignancies, the predominant form of radiation treatment for thyroid cancer consists of ^{131}I-ablation rather than external-beam radiation. Information on type of radiation treatment is reported in SEER from 1988 onward. Of 17,055 thyroid cancer patients diagnosed between 1988 and 2000, 45% had any radiation treatment, mostly in conjunction with surgery: 40% had ^{131}I-ablation and 5% received external-beam or combined modality radiotherapy. The remaining 55% had surgery alone. After ^{131}I-ablation, increased risks of stomach cancer (O = 8, O/E = 2.41, 95% CI = 1.04–4.75) and leukemia other than the chronic lymphocytic form (non-chronic lymphocytic leukemia (CLL)) (O = 11, O/E = 3.70, 95% CI = 1.84–6.61) were seen (Table IV). Only 2 salivary gland tumors were observed during the years 1988–2000, both after ^{131}I treatment. Risk of breast cancer did not vary by radiation treatment status (Table IV). While most ^{131}I is concentrated in the thyroid gland, much smaller amounts are concentrated in salivary glands, stomach, small intestine, bladder, and bone marrow. For the combined group of cancers in organs that concentrate ^{131}I, we found almost a 2-fold risk (95% CI = 1.29–2.76) among thyroid cancer patients given ^{131}I therapy (O = 29) (not shown). Exclusion of person-time and 90 second cancers that had been diagnosed 2–11 months after thyroid cancer diagnosis had little effect on the results (Table IV). Table V shows the reciprocal risk of thyroid cancer after cancers of selected sites by treatment status and time since first cancer diagnosis. Overall, cancer survivors who had any

TABLE IV – OCCURRENCE OF SECOND PRIMARY CANCERS, SELECTED SITES, FOLLOWING TREATMENT FOR THYROID CANCER[1]

No patients	Radiation treatment for thyroid cancer[2]					
	^{131}I only		Other radiation treatment		No radiation treatment	
	6745		1359[3]		8951[4]	
Second primary tumor	O	O/E	O	O/E	O	O/E
All sites[5]	236	1.14	53	1.21	394	1.19[6]
Salivary gland	2	3.90	0	—	0	—
Esophagus	2	1.22	2	5.05	0	—
Stomach	8	2.41[6]	1	1.27	9	1.74
Small intestine	1	1.46	1	6.81	2	1.79
Colon	12	0.76	3	0.84	29	1.09
Female breast[7]	53	1.18	9	1.12	95	1.25[6]
Bladder	7	0.92	1	0.58	14	1.19
Kidney	6	1.46	5	5.69[6]	10	1.56
Brain and CNS	4	1.56	0	—	7	1.80
Bones and joints	0	—	0	—	1	2.39
Soft tissue	1	0.95	0	—	1	0.63
Non-CLL leukemia	11	3.69[6]	0	—	6	1.28

[1]U.S. SEER cancer registries, 1988–2000. Details on radiation treatment modality have only been registered in SEER from 1988 onwards.–[2]Excluding person-years and cases occurring 2–11 months after the first cancer rendered the following results for all sites: ^{131}I only: O = 208, O/E = 1.16; other radiation treatment: O = 46, O/E = 1.27; no radiation treatment: O = 339, O/E = 1.17.–[3]Beam only (614), radioactive implants only (335), combination of beam with implants or isotopes (185), radiation treatment method not specified (42), radiation treatment recommended, unknown if administered (183)–[4]Surgery only (8861), refused radiation treatment (34), unknown (56).–[5]Excluding non-melanoma skin cancer.–[6]95% confidence interval does not include 1.0.–[7]For sex-specific cancers based on respective PY only.–O, observed number of cases; O/E ratio, observed over expected number of cases; CL, confidence interval. CLL, chronic lymphocytic leukemia.

TABLE V – OCCURRENCE OF THYROID CANCER AS A SECOND PRIMARY TUMOR BY TIME SINCE FIRST CANCER DIAGNOSIS AND RADIATION TREATMENT STATUS FOR THE FIRST CANCER[1]

First primary tumor	Risk of second primary thyroid cancer by time since first cancer diagnosis (yrs)							
	Any radiation treatment[2]				No radiation treatment[2]			
	<10		≥10		<10		≥10	
	O	O/E	O	O/E	O	O/E	O	O/E
All sites[3]	317	1.58[4]	80	1.59[4]	789	1.45[4]	180	1.09
Buccal cavity	20	2.32[4]	1	0.54	17	2.00	4	1.03
Esophagus	6	5.65[4]	0	—	0	—	0	—
Stomach	2	2.92	0	—	13	2.10[4]	0	—
Colon	0	—	0	—	81	1.27[4]	16	0.92
Lung and bronchus	35	2.76[4]	0	—	42	1.89[4]	7	1.61
Female breast[5]	81	1.25	18	1.38	199	1.45[4]	47	0.98
Prostate[5]	43	1.33	7	2.00	74	1.10	9	1.27
Bladder	2	1.00	0	—	34	0.99	9	0.90
Kidney	3	5.51[4]	0	—	37	3.18[4]	5	1.70
Melanoma	0	—	0	—	73	2.22[4]	20	1.53
Brain and CNS	10	3.03[4]	1	1.00	3	1.97	0	—
Thyroid	11	1.65	0	—	22	1.71[4]	17	2.06[4]
Hodgkin lymphoma	4	1.00	18	6.73[4]	5	1.82	5	4.48[4]
Leukemia	2	3.67	3	8.62[4]	30	2.45[4]	4	1.73

[1]U.S. SEER cancer registries, 1973–2000.–[2]All cancer cohort excluding non-melanoma skin cancer, radiation treatment, <10 yrs: 2,278,899 PY; ≥10 yrs: 526,196 PY; no radiation treatment, <10 y: 6,301,088 PY; ≥10 y: 1,701,861 PY.–[3]Excluding non-melanoma skin cancer;–[4]95% confidence interval does not include 1.0–[5]For sex-specific cancers based on respective PY only.–O, observed number of cases; O/E ratio, observed over expected number of cases; CI, confidence interval.

radiation treatment during the first course of treatment had 1.6 times the rate of thyroid cancer compared to the general population (O = 397). During the first 10 years, increased risks for thyroid cancer were seen for several cancer sites, irrespective of treatment status (Table V). Exclusion of autopsy or death certificate-based diagnoses, however, strongly reduced the high risks for thyroid cancer during the first 10 years for patients who had radiation treatment for cancers of the esophagus, lung, and kidney (O/E = 2.02, 1.00, and 0, respectively). Among long-term cancer survivors given radiation treatment, only patients with Hodgkin lymphoma (O = 18, O/E = 6.73, 95% CI = 3.99–10.64) and leukemia (O = 3, O/E = 8.62, 95% CI = 1.73–25.19) had strongly elevated risk of thyroid cancer (Table V). Long-term survivors of Hodgkin lymphoma whose initial treatment did not involve radiation were at increased thyroid cancer risk as well (O = 5, O/E = 4.48, 95% CI = 1.44–10.46).

Smoking

Lung cancer patients were at increased risk of thyroid cancer (O = 84, O/E = 2.10), although less clearly when autopsy and death certificate diagnoses of thyroid cancer were excluded (O = 50, O/E = 1.32). In contrast, after thyroid cancer we observed significantly reduced risks for lung cancer (O = 238, O/E = 0.87) and for the group of classic smoking-related cancers,[18] i.e., buccal

cavity (excluding salivary glands), lung, larynx, esophagus, pancreas, renal pelvis, and bladder (O = 387, O/E = 0.82).

Discussion

Our systematic evaluation of multiple cancers associated with thyroid malignancies revealed that the incidence of a second thyroid cancer was elevated after most first primary cancer sites and that the incidence of several cancers was increased after a first thyroid cancer. Several cancer sites showed significantly increased risks in both directions, including salivary glands, breast, prostate, kidney, scrotum, brain and CNS, and leukemia.

Methodologic aspects of the study and their implications for the interpretation of our findings deserve attention. O/E-based analyses use a general population reference group. Many competing factors may influence the risk of a second cancer, such as common etiologic factors, treatment effects, enhanced probability of detecting otherwise indolent cancers because of diagnostic workup for the first cancer, or intense medical surveillance.[15–17] In general, if the first cancer is associated with poor survival or elevated mortality from other conditions, a population comparison will underestimate second cancer risks, while diagnostic misclassification of metastases or recurrent disease as second primary malignancies and autopsies may result in overestimated risks, especially when the period between first and second tumors is long. For example, diagnostic misclassification of recurrent thyroid tumors has likely contributed to the increased risk of a second thyroid cancer in our analysis. The SEER program coding rules state that any new thyroid malignancy diagnosed more than 2 months after a first thyroid cancer should be recorded as a new primary. In clinical practice, however, such tumors are generally considered to be recurrences, except in rare occasions when histologic features suggest that they are truly independent primaries. Unfortunately, there is no objective way of determining whether 2 thyroid tumors are recurrences or new primaries. The estimate of second primary thyroid cancer risk among survivors of a first thyroid cancer is likely biased; the estimate of thyroid cancer risk among all cancer survivors, however, was not substantially affected. Metastases from differentiated thyroid cancer are rare, with lung and bone reportedly being the most common sites (affecting 2–10% of patients) in 2 large clinical series,[18,19] but thyroid metastases from other primaries occur more frequently,[20–23] sometimes mimicking primary thyroid cancer.[20,21] Since SEER registers the first course of treatment only, radiation treatment information may be incomplete. Finally, risk estimates likely are underestimated because some second cancers are missed due to patient migration outside of the cancer registry's catchment area and privacy rules prohibit record sharing within the SEER registries. Major strengths of the current analyses include the large number of patients and the long follow-up. This wealth of data permits evaluation of trends by latency and age, as well as detection of effects for less common cancer sites, and in several patient subgroups. Two other thyroid cancer cohorts included less than 7,000 survivors each,[24,25] compared to nearly 30,000 in our survey.

Thyroid cancer is predominant in women, and studies of reproductive factors have shown weak to moderate associations with thyroid cancer risk.[5] In agreement with U.S. and Israeli,[26–29] but not European[24,30,31] studies, we found small associations between thyroid and breast cancer, with no evidence of radiation-related risk.[25,32] Although breast and follicular thyroid cancers are among the malignancies included in the rare genetic syndrome Cowden's disease,[9] in our study, increased risks of breast cancer were seen after both papillary and follicular thyroid cancers. Because these familial cancer syndromes are uncommon, only a very small proportion of thyroid cancers are expected to be related to them.[10]

As in some other studies, we saw moderately increased risk of prostate cancer, mainly in the first decade after thyroid cancer diagnosis,[24,31] and of thyroid cancer after prostate cancer. Detection of otherwise indolent prostate and thyroid malignancies due to increased medical surveillance likely contributes to these observations. An investigation of prostate tumors showed overexpression of RET protein,[33] which plays an important role in thyroid carcinogenesis;[34] however, the relevance of this finding is not clear. A recent comprehensive analysis of cancer occurrences in Icelandic families (up to fifth-degree relatives) showed clustering of thyroid and prostate cancer.[35]

The joint occurrence of cancers of the thyroid gland and kidney has been reported previously.[24,25] The increased risk of kidney cancer after thyroid cancer was not specific to ^{131}I therapy, nor could it be explained by renal metastases from the thyroid cancer because they are too rare (<20 reported cases worldwide).[36] The reciprocal risk of thyroid cancer after kidney cancer decreased substantially with increasing follow-up time, suggesting at least a partial role of medical surveillance and/or misdiagnosed metastases, the thyroid being a common site for metastatic renal cell carcinoma.[22,23] A unifying biologic mechanism has yet to be identified. Other findings of related interest include a high prevalence of thyroid disorders among renal cell cancer patients,[37] a role of thyroid hormone receptors in kidney cancer,[38] a report of familial occurrences of papillary thyroid cancer and papillary renal carcinoma,[39] and increased risk of kidney cancer among relatives of thyroid cancer patients in Iceland.[35]

Unlike most other cancers, thyroid cancer is often treated with radiation treatment in the form of ^{131}I ablation. We were able to distinguish thyroid cancer patients who had different types of radiation treatment from 1988 onward and found increased risk of non-CLL after ^{131}I therapy. Leukemia is a well-known radiogenic malignancy.[40] Of extrathyroid organs, the bladder, stomach, small intestine, and salivary glands are exposed to the highest radiation doses from ^{131}I therapy in cancer patients.[41] For this combined group, including non-CLL, a 2-fold risk was shown after ^{131}I therapy. By site, we also found an increased risk for stomach cancer among patients treated with ^{131}I. In the full cohort of patients diagnosed with thyroid cancer between 1973 and 2000, 13 salivary gland cancers were observed for an almost 3-fold increased risk. Although the salivary glands are sensitive to radiation-induced cancer,[42,43] only 2 of the 13 patients with salivary gland cancer had received radiation treatment for their first thyroid cancer. Possibly, some patients received radiotherapy for benign head and neck conditions in the 1950s and 1960s, which has been linked with both salivary gland and thyroid tumors.[7,44] A pooled analysis from 3 European cohorts of 6,841 thyroid cancer patients (average follow-up = 13 years) reported a dose-response relationship with ^{131}I radiation activity for leukemia and for cancers of the salivary glands, colon, and bone and soft tissues.[25]

External head and neck radiation at young age is a strong risk factor for thyroid cancer.[7] Radiation treatment-related risks of thyroid cancer were only seen among long-term survivors of leukemia and Hodgkin lymphoma. Hodgkin lymphoma survivors not treated with radiation, however, also had a 4-fold risk of developing thyroid cancer, indicating a role of other factors, possibly including immune dysfunction, a known characteristic of Hodgkin's disease and several thyroid disorders.[45]

Based on very small numbers, we saw unexpected paired occurrences of thyroid and scrotal cancer. This constellation of tumors also occurred in male rats chronically exposed to acrylamide in drinking water,[46,47] but not in a mortality study of acrylamide workers;[48] however, few such fatal tumors were expected.[49] Two studies among psoriasis patients reported possibly treatment-related increased risks for thyroid and male genital nonmelanoma skin cancers.[50,51] Although our findings are intriguing, another explanation is chance, since the number of cases was extremely small. The 14-fold risk of tracheal cancer might be related to diagnostic misclassification of metastatic thyroid cancer presenting as endotracheal nodules.[52] The trachea is also in the radiation field for thyroid cancer radiotherapy. In contrast, we found *decreased* risks of smoking-related malignancies in thyroid cancer survivors.

This result may be explained by the repeatedly shown low prevalence of smoking among thyroid cancer patients.[53] Although several observations, including reduced thyroid stimulating hormone (TSH) levels, increased risk of goiter, and low body weight among smokers, as well as antiestrogenic properties of cigarette smoke, provide indirect clues about the biologic basis for this unusual finding, none provide a satisfactory explanation. In addition, it has been proposed that social class may confound the results.[53] In summary, thyroid cancer is associated with primary cancers of many different organs. Although enhanced medical surveillance likely plays a role, the 2-way positive associations between thyroid cancer and cancers of the breast, prostate, kidney, salivary glands, brain and CNS, scrotum, and leukemia suggest etiologic similarities and possible treatment effects.

Acknowledgements

The authors gratefully acknowledge Ms. R.E. Curtis and Drs. D.M. Freedman and J.F. Fraumeni, Jr., for helpful comments; Mr. D. Hacker, Ms. S. Merkle, and Mr. N. Appel for data management and analysis; and Dr. M.-L. McMaster for useful discussions. Dr. P. McCarron is supported by a career scientist award funded by the Research & Development Office for Health and Personal Social Services in Northern Ireland.

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